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MOLECULAR CHIRALITY AND SPONTANEOUS SYMMETRY BREAKING

Report on the occasion of awarding of V.I. Vernadsky Gold Medal of NAS of Ukraine

Introduction

A molecule that is not superimposable on its mirror image is found in two different enantiomeric forms, which we denote left- and right-handed. What is so striking is that life on Earth is homochiral; proteins occur in L-form and sugars in D-form. We do not know the origin of homochirality.

Molecular chirality was discovered in 1848 by Louis Pasteur. It was a young Pasteur who made the leap from crystal chirality, known since several decades, to molecular chirality. The concept of chirality was instrumental in establishing the tetrahedral valencies of the carbon atom, and has continued to play a key role in chemistry and molecular biology ever since.

Homochirality is an example of spontaneous symmetry breaking. Every sugar molecule made in a living organism is spiral in the same way, and quantum mechanical tunneling between the two enantiomeric forms is extremely slow, in fact non-existing. The parity symmetry can be ignored and the symmetry laws have been not repealed, but broken. There are several other examples of spontaneous symmetry breaking in physics and chemistry, of which one famous example is Bogolyubov's treatment of a Bose condensate [1]. This is a subtle and much less geometric symmetry breaking, as compared with chirality. Another famous example from physics is the introduction of order parameters to treat superconductivity by Ginzburg and Landau [2].

A chiral molecule is a source of optical activity. A linearly polarized light beam passing through an optically active medium will experience a rotation of the electric field vector. The direction of the rotation depends on the chirality of the active medium. An optical method that can differentiate between the two enantiomers of a chiral molecule is referred to as a chiroptical technique. Linear and circular dichroism, and light scattering techniques have been developed

to study molecules in gas and solution phase. The increasing demand for enantiomeric pure pharmaceuticals causes a need for efficient enantioselective analytical methods. Drugs that contain only one type of enantiomer are now the most common type of drugs. This is because different biological responses are obtained from different enantiomers of the same drug; one enantiomer produces the desired effect (eutomer) whereas the other has little effect or a serious adverse effect (distomer).

Chiral recognition in biology is based on the phenomenological three-point model, which states that at least three configuration-dependent interactions are required for a chiral selector to recognize enantiomers. Figure 1 shows the three-point model schematically.

Together with two young Ukrainian scientists, Kostiantyn Kulyk and Oleksii Rebrov, we decided to test the three-point model experimentally.

Experiment and results

Enantiomers of Methionine (Met), Phenylalanine (Phe) and Tryptophan (Trp) of ≥ 98 % optical purity were purchased from Sigma Aldrich and used in experiments without further purification. R-2-butanol (RB), S-2-butanol (SB), racemic 2-butanol, and 1-S-Phenylethanol (SP) of 99 % purity were purchased from Sigma Aldrich and used as target gases. Amino acids were dissolved in water/methanol/formic acid mixture (49:49:2 v/v/v) at a concentration of 0.04 mM. Molecular structure of amino acids and alcohols used in experiment are shown on Figure 2.

Experiments were carried out in MS/MS mode on the hybrid quadrupole time of flight (Q-ToF) mass spectrometer (Q-ToF 2, Micromass®) at the Department of Chemistry, University of Oslo (see Figure 3). Ions were produced by electrospray ionization source in positive mode of operation with 3 kV needle voltage and 100 °C source temperature. Precursor ions of studied amino acid were isolated by the quadrupole analyzer and transferred to a hexapole collision cell. After reaction with target gas ion products were transferred to ToF analyzer and detected with microchannel plate detector. Target gas was introduced to the collision cell via a needle valve. The gas

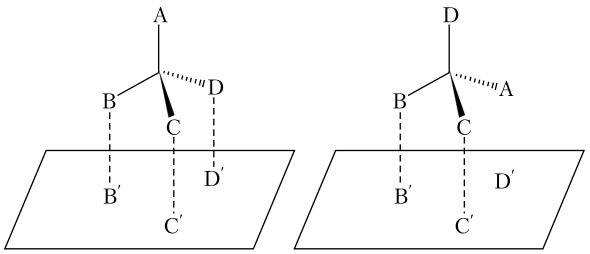

Figure 1. The chiral selector is represented by the plane. In order for the chiral selector to recognize the chiral molecule ABCD, three configuration-dependent points are required. This is fulfilled to the left, but not to the right

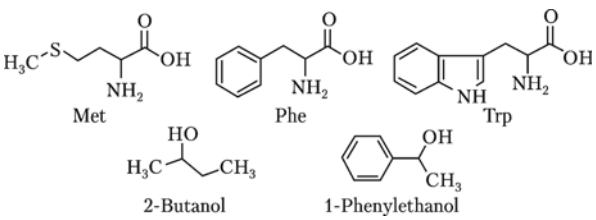

Figure 2. Molecular structure of analytes and target gases that were used in experiment

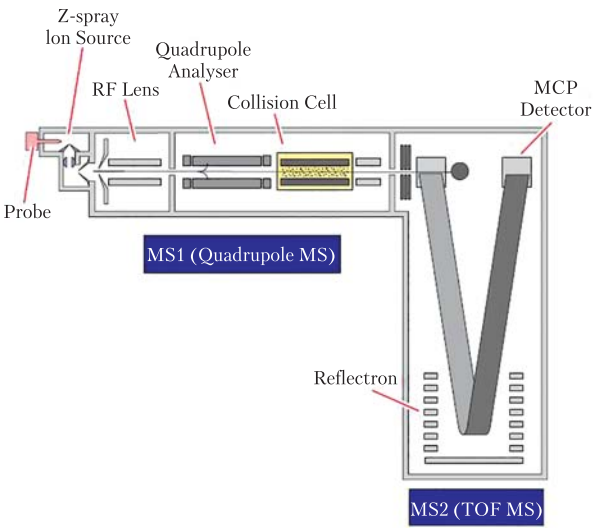

Figure 3. The Q-TOF instrument at the Department of Chemistry, University of Oslo. The ion source is of electrospray type. The ions are mass-selected and steered into the collision cell. Collision products, either as formed charged complexes or fragment ions, are analysed by the reflectron

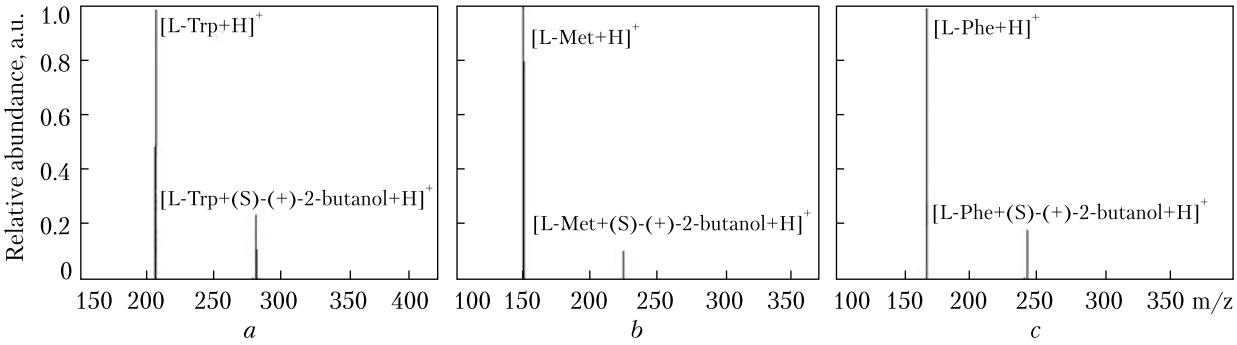

Figure 4. Mass spectra obtained from collisions of L-form of Trp (*a*), Met (*b*), Phe (*c*) with (S)-(+)-2-butanol at 0.1 eV collision energy. The parent ion (charged amino acids) is more abundant than the complex (diastereomer), but complex formation is clearly a very likely outcome of the interaction between projectile and target in the collision cell

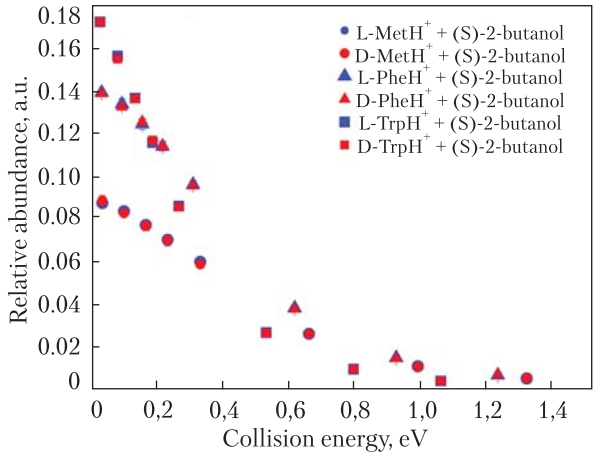

Figure 5. The abundance of complexes of L- and D-Met, L- and D-Phe, and L- and D-Trp with (S)-2-butanol as a function of collision energy. Within error bars, no difference in formation efficiency between the L- and D-forms are observed

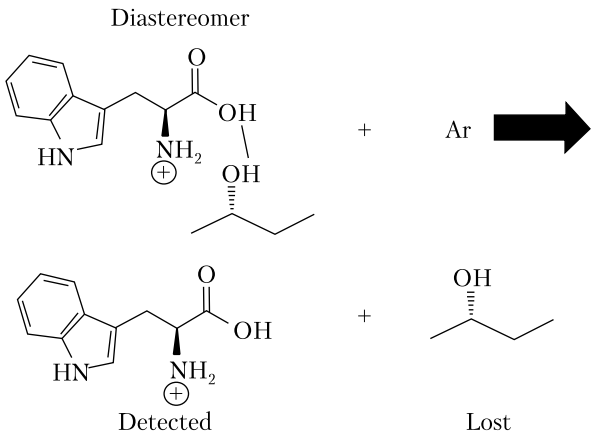

Figure 6. The amino acid Trp and butanol forms a charged complex which is introduced into the gas phase by the electrospray source. This diastereomer is now the projectile and the target is achiral argon atoms. In the collision process, butanol is lost and charged Trp detected

pressure in collision cell remained in a range of $7.02—8.25\times10^{-4}$ mBar during experiments with 2-butanol. The low pressure mode was used in order to study the basic mechanism of projectile-target complex formation in single collision mode. Collision energy range used in measurements was 0.1—4 eV in the laboratory frame of reference. The procedure of electrospray source cleaning with water : methanol solution (50:50 v/v) was performed after each measurement by spraying the solution through the system for several minutes.

The main product of an ion-molecule interaction for all amino acids used in the experiment was an adduct formation of analyte and target gas. Figure 4 shows the mass spectra recorded by the reflectron.

Based on the three-point model, one would anticipate that the combination of projectile and target chirality would affect the efficiency in complex formation, but as seen in Figure 5, this is not the case.

The results of the study of complex formation was published in ref. [3]. The study does not nec-

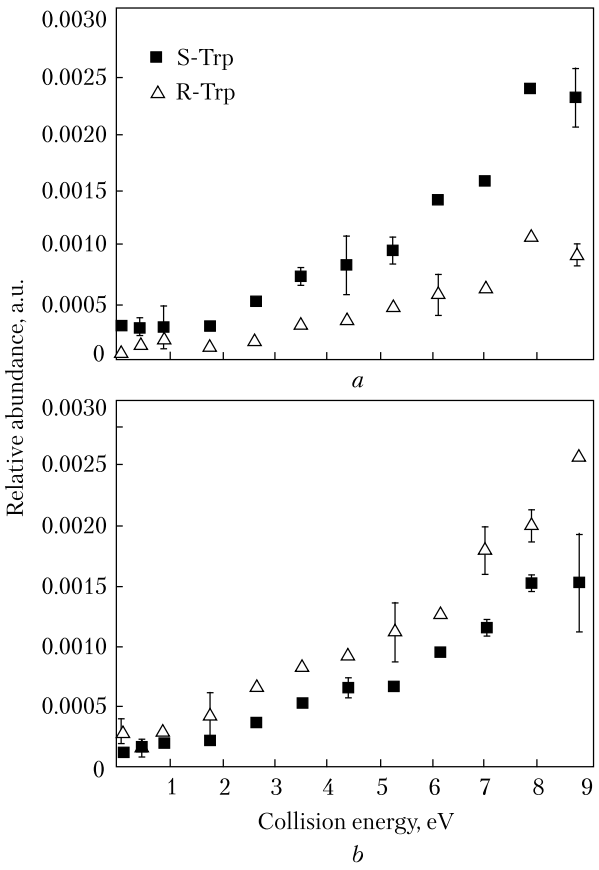

Figure 7. Relative abundance of protonated S- and R-Trp fragment generated in dissociation of proton-bound complex of S/R-Trp and S-2-butanol (*a*); R-2-butanol (*b*) as a function of collision energy. Here we used the S/R formalism instead of the L/D formalism for Trp, where S equals L and R equals D. The higher the abundance, the less stable is the complex

essarily invalidate the three-point model since we were unable to control the orientation of neither projectile nor target, which can lead to multiple hydrogen-bonded complexes with similar structure and energy.

We therefore tried another strategy, explained in Figure 6.

The results are shown in Figure 7, and taken from ref. [4]. It is clear from Fig. 7 that S-Trp is more stable when forming a complex with R-butanol, since it is destroyed less frequently as compared with R-Trp (Fig. 7*b*). The stability is reversed when S-butanol is used, and now the R-Trp + S-butanol complex is more stable than S-Trp + S-butanol complex.

Conclusions

The results presented here are the first of their type. It is the cleanest experiment ever carried out for chiral molecules; mass-selected ions at controlled energies in single collisions with a target gas. The fact that we did not see any effect of chirality in the experiments when we used charged amino acids as projectiles [3] does not invalidate the three-point model. It is quite possible that an experiment with orientation-controlled projectile and target would give a different outcome. Such experiments would be extremely difficult and have never been attempted. Instead we formed complexes of chiral molecules, so called diastereomers, and now clearly visible effects were noted [4]. These experiments give some qualitative support of the three-point model.

Acknowledgement

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